

## **Erectile dysfunction**

*'the persistent inability to attain and maintain an erection sufficient for satisfactory sexual performance'*

Incidence difficult to define

US population 52% of males aged 50-70yrs (Massachusetts Male Aging Study; mild, moderate and complete (10%))

In all studies incidence increases with age ? due to decline in smooth muscle concentration and age-related vascular leak

Geographically a/w high incidence of risk factors, namely smoking, obesity, diabetes, hyperlipidaemia and hypertension

### Aetiology

Psychogenic

Neurogenic

Central

MS

Stroke

Tumour

Parkinson's disease

Multi-system atrophy

Spinal cord transection/tumour

Peripheral

MS

Diabetes

Alcoholism

Uraemia

Sacral cord injury

Pelvic or retroperitoneal surgery

Hormonal

Hypogonadism

Hyperprolactinaemia

Hyperthyroidism

Cushings disease

Arterial

Arterial insufficiency due to CVS risk factors [DM, HT, hyperlipidaemia, smoking, obesity]

Post-traumatic arterial insufficiency (obliteration, fistula)

Venous

Peyronie's

Primary venous leak (rare)

Secondary venous leak

Shunting for priapism

Tunica albuginea injury after penile #

Drug-induced

Antihypertensives (esp. BB and thiazide diuretics)

Antidepressants

Antipsychotics

Antiandrogens

Antihistamines

Recreational drugs

Investigation (4)

Establish the nature of the problem

Identify any reversible causes of ED

Psychogenic

Drug-induced

Hormonal imbalance

Post-traumatic arterial insufficiency

Address risk factors

Manage impotence

Schedule

(i) History

a) Sexual history

Nature, onset and duration of symptoms

Libido, quality of erection, orgasm and ejaculation

Nocturnal, morning erections, non-coital erections, masturbation, relationship problems\*

International index for erectile function (IIEF; Rosen 1997)

can be used but quite cumbersome

\* psychogenic ED characterised by acute onset, morning and nocturnal erections, rigid non-coital erections and situational ED

b) Medical history

Concomitant medical problems

Previous retroperitoneal or pelvic surgery

Cardiovascular risk stratification (EAU GL)

Specific risk factors DM, hyperlipidaemia, hypertension, smoking status, BMI

No contraindications to sex if:

Asymptomatic + <3 risk factors

Post-stenting or mild angina

Mild CCF (NYHA1)

Controlled hypertension

c) Drug history

(ii) Physical examination

Secondary sexual characteristics

Groin examination and pedal pulses

Genital examination

Size and shape (?chordee)

Peyronie's

Penile sensation

Bulbocavernosus reflex

DRE

Perineal sensation

Anal reflex and tone

Prostate examination if over 50 yrs

(iii) Laboratory testing

Fasting sample

Testosterone (bioavailable or free-T better to diagnose hypogonadism)

Lipids

Glucose

Optional

PSA in men > 50 yrs with >10 yr life-expectancy

Prolactin

Hyperprolactinaemia quite rare

Galactorrhoea, gynaecomastia, ED

TFTs in those with clinical features of hypo or hyperthyroidism

In the vast majority of patients the above schedule sufficient. With the exception of patients with psychogenic ED, drug-induced, post-traumatic arterial insufficiency or hormonal imbalance ED cannot be cured. Thus a goal-directed approach is entirely appropriate. Additional tests:

#### Nocturnal penile tumescence

Confirm psychogenic ED

Home testing; 2 rings (base and subcoronal)

> 60% rigidity at subcoronal for > 10 minutes excludes organic cause

#### Intracavernous injection +/- stimulation

Test and teach response to injection therapy

Alprostadil 10-20ug intracavernosally

Some patients inhibited by needle – may require additional stimulation

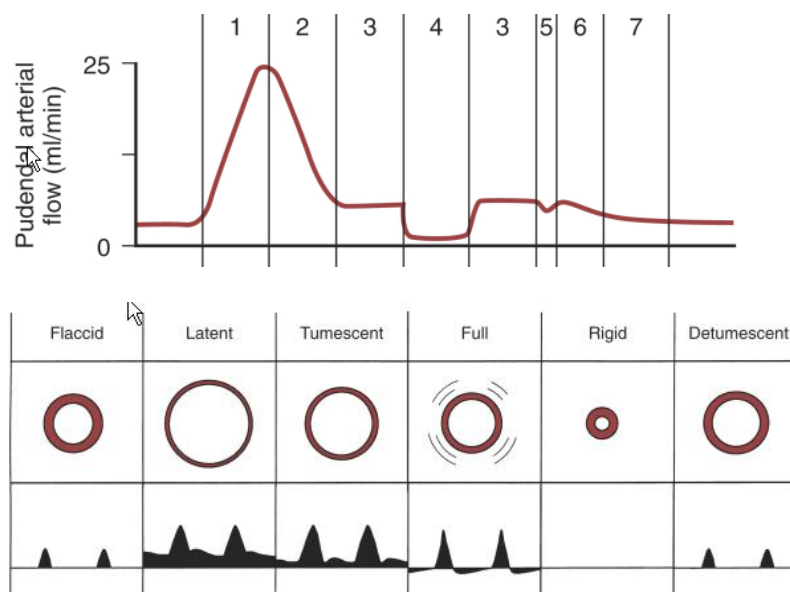
#### Duplex ultrasonography

Assessment of vascular flow in penis during erection

Suspicion of primary venous leak or post-traumatic arterial insufficiency

PGE1 augmented erections

Duplex performed 5mins after injection (latent) through to cessation of flow (rigid)



Arterial insufficiency	Peak systolic velocity < 25cm/s*
Venous leak	PSV consistently > 25cm/s and end-diastolic velocity > 5cm/s

\* if post-traumatic arterial insufficiency suspected and arterial re-vascularisation considered, DICC should be performed to exclude venous leak. If normal arteriography road map

#### Dynamic infusion cavernosometry and cavernosography (DICC)

Intracavernous injection of PGE1

Infusion of normal saline and continued pressure measurement

Normal = < 5ml/min required to maintain rigid erection

Pressure drop > 100mmHg after cessation

Rarely performed – Doppler USS more common

Cavernosography occasionally performed to exclude leak prior to revascularisation

### **Management of erectile dysfunction**

3 components

Management of 'curable' ED

Address lifestyle factors

Manage impotence

#### (i) Management of 'curable' ED

Hormonal abnormalities referred to endocrinologist

MRI or CT of pituitary fossa in hyperprolactinaemia

Testosterone replacement therapy acceptable in men with LOH and ED in whom DRE and PSA are normal

Psychosexual counselling in patients with severe psychogenic ED

Post-traumatic arterial insufficiency

Staging investigations

Doppler USS, cavernosogram and arteriogram

Donor vessel usually inferior epigastric grafted onto dorsal penile artery. Long-term success rates ~25% at 12-24 months

Penile venous surgery

Venous surgery for venous leak a/w poor outcomes due to persistent leakage

70% success reported (Lue) in patients < 40 yrs with congenital (maldeveloped crura and cavernous leak) and post-traumatic venous leak

Ligation of deep dorsal vein and both crural bases

#### (ii) Address lifestyle factors

CVS risk factors – refer to cardiologist

Elevated fasting glucose – refer endocrinology/GP

Elevated lipids – refer GP

Smoking cessation self-help groups/new leaf

Promote exercise

Some evidence that modification of CVS risk factors can have significant impact on ED

Atorvastatin in lone hyperlipidaemia Saltzman 2004

Switch to losartan in hypertension Caro 2001

However RCT data required and at present most patients receive goal-directed ED therapy in addition to lifestyle modification

#### A. First-line therapy

##### (i) PDE5 inhibitors

Inhibition of PDE5 elevates cGMP facilitating smooth muscle relaxation

**Not erectogenic** – require intact nerve pathways and stimulation

Sildenafil (Viagra, Pfizer), Vardenafil (Levitra, Bayer-GSK), Tadalafil (Cialis, Lilly)

Parameter	Sildenafil 100mg	Tadalafil 20mg	Vardenafil 20mg
Onset	30 mins	30 mins	30 mins
Tmax	1 hr	2 hr	45 mins
PDE5 inhibition*	+	+++	++++
Half-life (T1/2)	3.8	17.5	3.9
Fatty meal	Impairs action	No effect	Impairs action
Duration action	12 hrs	36 hrs	12 hrs
Doses	25,50,100mg	10,20mg	5,10,20mg
Efficacy @ max**	84%	81%	80%
Cost (8 tabs)	£47	£54	£47

\* All highly potent drugs – no difference in real-world effect

\*\* No direct comparison studies

Adverse event	Sildenafil	Tadalafil	Vardenafil
Headache	12.8%	14.5%	16%
Flushing	10.4%	4.1%	12%
Dyspepsia	4.6%	12.3%	4%
Nasal congestion	1.1%	4.3%	10%
Dizziness	1.2%	2.3%	2%
Abnormal vision	1.9%		<2%
Back pain		6.5%	
Myalgia		5.7%	

NB. Sildenafil a/w blurred vision, blue vision, hypersensitivity (PDE6 cross-inhibition)

#### Contraindications to PDE5i

Nitrates All PDE5is absolutely contraindicated in patients taking nitrate preparations (including poppers)

a-blockers Vardenafil and alpha-blockers banned in US  
Sildenafil not within 4 hrs of an alpha-blocker

#### Drug interactions

PDE5i effect increased erythromycin, ketoconazole, itraconazole, HIV meds (CYP3A4 enzyme pathway)

PDE5i effect decreases rifampicin, phenytoin, carbamazepine

## NHS PDE5i (mark prescription SLS)

## Neurogenic ED

MS, DM, Parkinson's disease, polio, spina bifida, spinal cord injury

Dialysis or renal transplant

Prostate cancer/TURP/radical pelvic surgery

Rx prior to September 1998

Severe mental stress

## (ii) Other oral agents

Apomorphine	Centrally acting dopamine agonist D1 and D2 receptor specific Efficacy originally thought to be 30-50% Well tolerated (N+V) no BP drop ? first-line in those with nitrates Withdrawn from UK in 2006
Phentolamine	Centrally acting alpha blocker ~50% efficacy. Not licensed
L-arginine	NO donor. Not licensed
Yohimbine	Centrally acting alpha-2 adrenoceptor blocker No improvement vs. placebo
Trazodone	Serotonergic and alpha blocker No improvement

All of above except apomorphine not recommended. Apomorphine withdrawn. PDE5i therefore first and only oral option. New agents with potential activity comprise guanylate cyclase activators, potassium channel activators and Rho-kinase inhibitors.

## (iii) Topical therapy

Nitroglycerine, alprostadil and papaverine gels all used

Absorption thro' tunica albuginea poor

Even with enhancers results poor (33% responders) and skin irritation common

## (iv) Vacuum constriction device

Highly effective > 90% erections sufficient for intercourse

Drop-out rates high ~50% usage at 2 yrs

Complications pain, bruising, no ejaculation, cool paraesthetic penis impaired spontaneity, pivoting of soft penis below constriction ring, occasionally skin necrosis

B. Second-line therapy

## (i) PDE5i salvage

Consider failure if 4 attempts with maximum dose have not worked

Daily dosing of PDE5i may improve benefit, but most studies have shown only a modest benefit (IIEF score reported rather than absolute success rates)

Similar reports for adjuvant T in hypogonad PDE5 non-responders  
(<10% of patients with ED hypogonad)

(ii) Intracavernous injection

Alprostadil, papaverine and phentolamine, or combinations

Alprostadil is a synthetic prostaglandin E1 analogue which acts on  
adenylate cyclase-cAMP pathway

Papaverine is a non-selective PDE inhibitor which prevents cAMP and  
cGMP breakdown

Phentolamine alpha-adrenoceptor agonist which reduces cytosolic IP3

Parameter	Papaverine	Pap&Phent	Alprostadil	Trimix
Dose	7.5 – 60mg	0.1-1ml	1- 60ug	0.1-1ml
Efficacy	50%	70%	85%	92%
Pain	-	-	15-30%	2-20%
Priapism	5%	8%	1%	2%
Fibrosis	7%	7%	3%	2%

Only Alprostadil (PGE1) licensed in UK. If pain is a particular problem,  
Trimix could be considered on a named patient basis

Overall failure of injection therapy 5-10%: 30% of these may be  
salvaged with combination PGE1 and PDE5i

Sickle cell disease but not anticoagulants contraindicated with ICI

(iii) Intraurethral therapy

125ug-1mg alprostadil via MUSE applicator

Efficacy ~50% only with higher doses (start at 500ug)

Pain (33%) dizziness (10%) urethral bleeding (5%) common Ses

C. Third-line therapy

Penile implants

Malleable

Mechanical

Inflatable (two-piece or three-piece)

AMS 700CX/CXM and Mentor alpha I most commonly inserted (both  
three-piece inflatable). Typically inserted via infrapubic or penoscrotal  
incisions. Subcoronal only for malleable prostheses. Traditional bougie  
sizing of corpora cavernosa oversizes by ~2cm. Reservoir best placed  
in retropubic place to avoid autoinflation.

Counselling

Partner and wife ideal

'Erect' penile length shorter than natural erection (glans soft)

Mechanical failure requires re-operation or removal

Infection & erosion mandate removal

Re-implantation often smaller due to scarring

Overall satisfaction rates 80% (best for three-piece)

Mechanical failure and cost

3-piece > 2-piece > malleable

AMS 700CX/CXM failure rates 7-16% at 5 yrs follow-up

Best paper Wilson et al 2007 – revision-free survival 60% at 15 years (infection rate 9%; therefore mechanical failure rate ~30% at 15 years)

Infection

Early infection GNB, late infection GPB

<5% for two most popular implants

2-3% for broad-spectrum antibiotics (gentamicin and vancomycin 1 hr pre-op)

1% for antibiotic impregnated implants

9% infection rate in spinal cord injury

No increased infection rate in diabetics

Infected graft

Removal, antibiotics and re-implant after 3-6 months, but significant scarring and fibrosis

Single stage removal, antibiotic lavage and re-implant a/w infection rates of ~20% (Mulcahy 2000)



## Appendix

### EAU cardiac risk stratification

Low-risk	Sexual activity OK
Intermediate-risk	Cardiac investigation first
High-risk	Sexual activity not recommended

Low-risk category	Intermediate-risk category	High-risk category
Asymptomatic, < 3 risk factors for CAD (excluding gender)	≥ 3 risk factors for CAD (excluding gender)	High-risk arrhythmias
Mild, stable angina (evaluated and/or being treated)	Moderate, stable angina	Unstable or refractory angina
Uncomplicated past MI	Recent MI (> 2, < 6 weeks)	Recent MI (< 2 weeks)
LVD/CHF (NYHA class I)	LVD/CHF (NYHA class II)	LVD/CHF (NYHA class III/IV)
Post-successful coronary revascularization	Non-cardiac sequelae of atherosclerotic disease (e.g. stroke, peripheral vascular disease)	Hypertrophic obstructive and other cardiomyopathies
Controlled hypertension		Uncontrolled hypertension
Mild valvular disease		Moderate-to-severe valvular disease

*CAD, coronary artery disease; CHF, congestive heart failure; LVD, left ventricular dysfunction; MI, myocardial infarction; NYHA, New York Heart Association.*

### New York Heart Association classification of CCF

Class I: patients with no limitation of activities; they suffer no symptoms from ordinary activities.

Class II: patients with slight, mild limitation of activity; they are comfortable with rest or with mild exertion.

Class III: patients with marked limitation of activity; they are comfortable only at rest.

Class IV: patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest

### IIEF Questionnaire

International index of erectile function

Typically short-form 5 used (IIEF-5)

5 domains/questions covering erection/sexual performance:

Achievement

Adequacy

Maintenance after penetration

Maintenance to orgasm/ejaculation

Satisfaction

Points given in range 0-5 (5 = best outcome)

0-7 Severe ED

22-25 No ED